

charged with reviewing issues raised in the Research Agenda regarding concepts of extrapolation of laboratory study results to actual use of wireless communication technology by humans. The Working Group will consider the following aspects of extrapolation, and it is recommended that all investigators who apply to the program consider these issues in developing proposals as well:

- How can dosimetric parameters be extrapolated from *in vitro* or animal studies to human exposures?
- How are results of *in vitro* and *in vivo* studies used to evaluate risk of human exposures?
- How can *in vitro* and *in vivo* studies using a variety of endpoints or tissues be extrapolated to assess potential risk associated with a specific endpoint and tissue?

The rationale for considering these issues is threefold:

- A framework for the consideration of *in vitro* and *in vivo* studies in an assessment of the potential human health effects of wireless communication technology is required;
- Specific to studies involving RFR, concepts such as dosimetric scaling, tissue extrapolation, and dose extrapolation must be considered when conducting and interpreting studies directed at understanding potential effects of wireless communication technology; and
- The extent to which diverse endpoints measured *in vitro* or *in vivo* can be used to assess specific potential risks or methods for mitigating such risks will be crucial to the WTR's risk evaluation and risk management functions.

The concept of extrapolation is complex, covering both theoretical models as well as, more recently, real life examples where data from cells in culture, animals and humans are available and mechanisms of action are understood. Several recent reviews on the subject have been published, and the concept of extrapolation is important in risk evaluation at the regulatory level (Strom, 1987; Vainio and Cardis, 1992; Toxicity tests in animals, 1993). Adding to the already complex nature of this topic are particular problems related to the study of RFR and the assessment of potential health effects of wireless communication technology. For example, the

need to consider dose and exposure extrapolations will require both biological and engineering expertise. Additionally, extrapolation of data from diverse endpoints to a very specific outcome is a unique problem possibly requiring new approaches and models.

The complexity of this problem makes clear the need for the introduction of new ideas and the involvement of an interdisciplinary team in the development of a position paper on this subject. The WTR has chosen to approach the completion of this task through the sponsorship of a workshop to be chaired by the Extrapolation Working Group. The Working Group will be made up of recognized experts in the field of risk assessment and extrapolation and include members of the Toxicology and Dosimetry Working Groups. The workshop format will allow for the introduction of a variety of ideas in the form of invited presentations as well as the formulation of a concept paper by the working group. Both the presentations and the concept paper will be submitted for publication in a peer-reviewed journal. This process will, therefore, both support the WTR risk evaluation and management programs, and add to the general knowledge base in this field.

3.5 Research Priorities

The Research Agenda presents a thorough and detailed review of available studies of potential genotoxic and carcinogenic effect of RFR. The Research Agenda also contains a listing of available reviews of the biological effects of RFR including those by the National Council of Radiation Protection and Measurements (NCRP, 1986) and the World Health Organization (WHO, 1993). In addition, the WTR is currently sponsoring critical reviews of available literature on potential genotoxicity (including DNA damage), carcinogenicity, and “non-genotoxic” effects (e.g., alterations of protein synthesis and membrane effects) of RFR. Finally, the WTR conducts an ongoing literature surveillance program directed at the assessment of adverse health effects of RFR with special emphasis on studies directly relevant to wireless communication instruments. In general, conclusions enumerated in the Research Agenda have not be altered by the assessment of studies completed subsequent to its publication or WTR-

sponsored expert critical literature reviews. As summarized in the Research Agenda the following conclusions were reached after reviewing the available literature:

- There appears to be a threshold for biological effects of RFR in animals at a SAR of 2 W/kg.
- Studies involving RFR vary greatly in terms of protocol quality, dosimetric evaluation, exposure system, and control of confounders such as temperature.
- While a large number of studies exist which evaluate the biological effects of RFR, few *in vitro*, *in vivo*, or long-term animal studies exist that are directly relevant to exposures related to human use of wireless communication instruments.

Based on this assessment of the available literature, the WTR toxicology program will include studies in areas of research relevant to the evaluation of potential carcinogenic effects of RFR associated with wireless communication using a regulatory paradigm.

3.5.1 Genotoxicity Studies

The WTR toxicology program will focus its efforts on study areas identified through the surveillance program and selected as relevant to the creation of a database that is required for regulatory assessment of RFR exposures associated with wireless communication instruments. Proposals have been solicited for the study of RFR at cellular telephone frequencies using the SCG assay *in vitro*. The WTR is currently reviewing proposals submitted in response to the RFP for these studies and will announce funding decisions by September 1. The WTR anticipates that *in vivo* studies utilizing the SCG assay will be initiated upon the development of an appropriate exposure system. Additionally, the WTR will sponsor studies aimed at the evaluation of protocol variations on the results observed using standard agents in the SCG assay. Investigators interested in conducting *in vivo* studies using the SCG assay should wait for publication of the relevant RFP.

Genotoxicity studies involving use of standardized tests will focus on those described in the accompanying RFP. Study selection and publication of an RFP involving *in vivo* studies will await completion of a sufficient portion of the *in vitro* studies to allow a preliminary assessment of the results of these studies. Conduct of *in vivo* studies will also require the completion of an appropriate exposure system.

3.5.2 Sub-Chronic and Chronic Animal Studies

The WTR toxicology *in vivo* research program will focus on the collection of information needed design long-term animal bioassays capable of assessing all important dosimetric parameters. The WTR effort will include review of protocols used in completed studies involving long-term exposures to electromagnetic radiation. A critical review of available studies involving RFR frequencies is currently underway and will be submitted for publication when complete.

Laboratory research will focus on completion of a series of sub-chronic animal studies, which will be initiated upon completion of an *in vivo* exposure system. Sub-chronic animal studies will be used to evaluate general toxicology related to use of the appropriate exposure apparatus, as well as the effects of different wireless technologies and dosimetric parameters. Endpoints to be assessed will include general toxicology, a thorough pathologic evaluation, and other endpoints selected after consultations with experts. Emphasis will be placed on the evaluation of signs of tissue-specific toxicity with special emphasis on tissues identified as relevant to epidemiological evaluation (e.g., brain, salivary and parotid gland; see sections 5.1.2 and 7.2.4 for discussion). RFPs for sub-chronic and chronic animal studies will be published when study design decisions have been finalized. Investigators interested in conducting sub-chronic studies or long-term animal bioassays should await publication of RFPs specifically requesting such proposals.

During the summer of 1994, as part of the WTR's ongoing surveillance program, European and American research was identified regarding potential health effects of cellular phones. Three papers presented at the annual Bioelectromagnetic Conference in Copenhagen and preliminary research in the United States reported the potential for cellular phones to interfere with implanted pacemakers. These reports generated valid questions on the health effects of wireless communication technology and indicated the need for further investigation to aid decisionmakers. In a meeting with the FDA it was determined that the WTR should conduct clinical studies investigating the possible interactions between cellular telephones and pacemakers.

Clinical studies were not originally considered in the Research Agenda nor in the overall health risk evaluation research plan. It was described, however, as a discipline to be considered when evaluating existing data and in defining both the overall research program and the health risk evaluation research plan. The Research Agenda defined and described the utility of clinical studies for evaluating public health risk as follows:

“Clinical studies or clinical trials are tightly controlled, prospective evaluations of human subjects exposed to a particular drug, device, or intervention. Usually, clinical studies are designed specifically to investigate issues of safety and efficacy (Temple, 1982). Sometimes, clinical studies are useful in defining exposure paradigms for epidemiological studies.”

In response to public and government agency concerns, and consistent with the WTR's commitment to the rapid identification and response to potential adverse health effects of wireless communication instruments, clinical research has been incorporated into the WTR program.

4.1 Cellular Phone Pacemaker Interaction Studies

The program developed for the clinical study of the potential interference between cellular phones and implanted pacemakers is following a three-phase approach. The first phase included the development of a protocol by a multi-disciplinary committee of experts, chaired by Dr. Carlo of WTR. Team members included scientists and physicians from the FDA, the University of Oklahoma, the Mayo Clinic, Mt. Sinai Medical Center in Miami, the George Washington University Medical Center, the Health Instruments Manufacturers Association (HIMA) and the Cellular Telecommunications Industry Association (CTIA). WTR's Peer Review Board, coordinated by the Harvard University School of Public Health, Center for Risk Analysis, also reviewed the protocol.

The second phase of this program includes the implementation of the clinical studies, according to the protocol entitled, "A Clinical Study to Assess the Potential for Hand-Held Wireless Telephones to Interfere with Implanted Pacemakers." The study will follow those guidelines presented in WTR's previously released Research Agenda and GCPs. Dr. Donald McRee, WTR's Director of Extramural Research, will oversee quality control of the project.

Phase three will focus on the interpretation of the study results. Due to the technical nature of the outcomes of the study, an expert panel of cardiologists has been convened to address the issue of the clinical significance of pacemaker responses. They will assist WTR in assessing the public health impact of the study's findings.

4.2 Research Priorities

Current clinical research regarding pacemaker cellular phone interactions will consider all cellular telephone technologies expected to be in use by the end of 1995. This includes analog and digital technologies operating in the 800 to 900 MHZ band as well as some digital technologies operating in the 1800 to 2200 MHZ band.

The current clinical research focuses on pacemakers; however, pilot studies underway consider possible interactions between cellular phones and cardiac defibrillators as well. If large scale clinical studies of defibrillator patients are required, specific requests for proposals will be issued.

5.0 TIER II STUDIES - EPIDEMIOLOGY

Under the WTR program, Tier II epidemiology studies are considered in the context of both post-market surveillance and as tools to test specific cause-effect hypotheses to supplement Tier I experimental studies. The WTR believes that neither experimental studies nor epidemiological studies alone can provide a solid basis for assessing the potential public health impact of wireless communication technology. Therefore, results of studies from each of these distinct disciplines must be considered and interpreted in the context of the other, and answers regarding public health risk must follow from a weight-of-evidence evaluation.

5.1 Progress to Date

An extensive effort has also been launched by the WTR to provide for ongoing prospective mortality and morbidity surveillance of cellular telephone users. Surveillance cohorts have been established and it is expected that more than eight million phone users will be included by the end of 1996. Systems are in place to provide for timely record linkage with existing mortality and morbidity registries in the United States. It is also anticipated that new technologies will be added to the surveillance effort as they come into use.

5.1.1 Epidemiology Surveillance Studies

The WTR has an epidemiology literature surveillance program currently in place. The purpose of this surveillance is to monitor general epidemiological studies, disease-specific studies, and exposure-specific studies which may provide additional information about hypotheses and

measurement outcomes in WTR-sponsored epidemiological studies. Periodic record-linkage studies of user cohorts will also be done in the context of ongoing surveillance.

5.1.2 Disease-specific Hypothesis Testing Studies

A working group of scientists in cancer and epidemiology has made recommendations to the WTR regarding meaningful outcomes for case-control studies of cellular telephone users. They considered current dosimetric modeling results of SAR with hand-held cellular phones and the likely types of tissues to be affected. The group came to consensus on the following tumors on which to focus study outcomes: gliomas, meningiomas, nerve sheath tumors (including acoustic neuromas); parotid gland tumors, and adult-onset leukemia.

5.1.3 WTR Study Assistance

The WTR has endeavoured to assist potential investigators in conducting research focused on WTR priorities. Phone user records can be made available to investigators through the WTR. Epidemiology Resources, Inc. is the custodian of the billing records from the various cellular telephone carriers. Use of these records to define cohorts and quantify individual phone usage as part of epidemiological studies is encouraged; however, access to them must be coordinated through Epidemiology Resources, Inc. The following two sections provide summaries of pilot studies and other experience that may be helpful to potential investigators.

5.1.4 Usefulness Of Questionnaire Information

A pilot study of nearly 4,000 cellular phone subscribers conducted by Epidemiology Resources, Inc., has established a good correlation between answers supplied by the subscribers and their telephone billing records. Based on these results, WTR is prepared to accept the use of questionnaires to help quantify usage and address confounding issues in epidemiological studies.

5.1.5 Exposure Assessment Considerations

A working group of experts in epidemiology and RFR dosimetry addressed important exposure issues relevant to wireless communication instrument users. The report of this working group entitled "Assessment of Radiofrequency Exposure for Epidemiologic Studies of Wireless Communication" is available from the WTR upon request. They studied a number of cellular technology and human exposure considerations designed to provide guidance in epidemiological studies. The issues and the working group's subsequent recommendations include:

- Length and duration of phone calls: For example, is one 10-minute phone call equal to 10 one-minute phone calls? The group determined that the duration of calls and frequency of calls should be considered separately;
- Use of billing records: Studies based on billing records can be supplemented by studies based on questionnaires to address confounding;
- What does cumulative use per month mean? Cumulative use should be supplemented by other surrogate exposure metrics;
- Cell site density and power: A weighting scheme of power transmitting from the phones determined by cell site density (and therefore geographic area) should be developed; and
- Alternative exposure metrics: Internal consistency for varied exposure metrics could be an important consideration regarding cause and effect.

5.2 Research Priorities

The WTR epidemiology program will focus on investigations involving cohort and case-control studies. Cohort studies will be used to assess general mortality and morbidity of analog and digital cellular telephone users in the United States and Europe. Case-control studies will focus on tumor types or locations, specifically: gliomas, meningiomas, neuromas (including acoustic neuromas), adult-onset leukemia, and tumors of the salivary glands (including the parotid gland).

5.3 Study Criteria

The following criteria should be addressed by investigators seeking to conduct epidemiology studies under the WTR program.

5.3.1 Consider Relevant Human Exposure

Investigators must show an appreciation for important exposure issues relevant to wireless communication instrument users in their study designs. Included should be issues such as the importance of handedness in determining exposure, the importance of potential confounders such as wire-rimmed eye glasses, and the role of variables such as location of telephone call with respect to proximity to a base station.

5.3.2 Studies Should Include Only Meaningful Outcomes

Investigators should provide a scientific rationale for including specific outcome measures in epidemiology studies. Consideration should be given to such issues as the types of tissues likely to be affected by cellular telephone use considering current dosimetric modeling results.

5.3.3 Studies Should Employ Well-Considered and Appropriate Exposure Measures

Investigators should include a rationale and evaluation of exposure measures to be used in epidemiology studies. Consideration should be given to such issues as the difference in terms of dose between 10 one-minute phone calls and one 10-minute phone call, internal consistency of measures within the same study, and dose-response.

6.0 PROPOSAL REQUIREMENTS, PROCEDURES, AND DEADLINES

Proposals will be accepted from any qualified investigator. Investigators who have had previous contractual agreements with the WTR, have served on or are currently serving on WTR expert panels, or are members of other WTR support groups are not restricted from submitting proposals since they have served only in an overall advisory capacity to the WTR and have not participated in the detailed design of research projects which are being solicited.

6.1 Quality Assurance Program

The WTR requires that all studies performed under its program must be conducted using good scientific practices. The guidelines to ensure that data are valid, reproducible, and accurately represent the outcome of the studies are described within three specific categories:

- Good Laboratory Practices for Nonclinical Studies (GLPs);
- Good Epidemiology Practices for Occupational and Environmental Epidemiologic Research (GEPs); and
- Good Clinical Practices (GCPs).

The guidelines presented in the documents referenced in Appendix B must be followed in the design and conduct of research projects under the WTR program. Copies of these documents are attached in the Appendix, and a brief summary of some important elements is presented.

6.2 Proposal Review Process

The review process will consist of an initial administrative review by the WTR to assess the extent to which each proposal meets the requirements of the RFP. Proposals which are deemed incomplete or non-responsive to the RFP will be returned to the investigators without further action. The scientific merit of proposals deemed complete and responsive to the RFP will be reviewed by review committees (made up of members of WTR expert panels and working

groups) that will be established on an ad hoc basis. Recommendations of the review committees will be submitted to the WTR which will select proposals to be considered for funding. The established Peer Review Board will review these proposals and submit recommendations. Final decisions on funding are the responsibility of the WTR.

The review committees will evaluate applications according to the following criteria:

- Relevance of the proposal to the objectives of the RFP;
- Scientific merit of the research approach, methodology, analytical methods, and statistical procedures;
- Qualifications and research experience of the principal investigator and staff, particularly, but not exclusively, in the area of the proposed research;
- Adequacy of effort on the project by scientific and technical staff;
- Adequacy of facilities;
- Appropriateness of the proposed budget and time to complete the research; and
- GLP compliance and Quality Assurance (QA) Program.

6.3 WTR Timetables

The WTR process is open and continuous. Proposals will be accepted immediately pursuant to this RFP. Funds will be dispersed based upon merit, and timeliness. If adequate work is committed in a specific topic area, late proposals in that area will be returned to the potential investigators, unreviewed. Only proposals that meet the requirements articulated herein will be considered for funding.

7.0 SPECIFIC REQUESTS FOR PROPOSALS

The WTR, based on the rationale and research priorities outlined in this document, has developed the following RFPs. As the risk evaluation and management programs develop, information from WTR-sponsored research is collected, and new areas of relevance to the

program are identified, the WTR anticipates that new RFPs will be developed and circulated. However, the WTR risk evaluation program has clear and specific objectives. Investigators are, therefore, advised to become familiar with the WTR's program by obtaining and reading literature published by the WTR (see section 1.1) especially the Research Agenda. In addition, investigators submitting proposals should become familiar with the specific proposal requirements listed in section 6.

7.1 Request for Proposals - Tier 1 *In vitro* Studies

7.1.1 *In Vitro* Assessment of Potential Genotoxicity of 837 MHz Radiofrequency Radiation (WTR-TRP-003)

Subject Area: The WTR, in response to the needs of its toxicology research program, is soliciting proposals for specific research projects. The following background information and proposal details are intended to assist investigators interested in submitting proposals to perform tests involving 837 MHz RFR. Tests to be conducted will include bacterial and *in vitro* mammalian mutation assays and a chromosome aberration assay in human peripheral blood lymphocytes.

Background: In August 1994, the SAG published a research plan entitled "Potential Public Health Risks from Wireless Technology: Research Agenda for the Development of Data for Science-Based Decisionmaking," hereafter referred to as the Research Agenda. The Research Agenda outlined guiding principles for the development of a complete, relevant, credible, and rigorous scientific program for the evaluation of potential human health risks associated with the use of wireless technology.

Guiding Principle Number One of the Research Agenda outlined a three-tiered concept to be used in evaluating the priorities of the risk evaluation research plan. Potential carcinogenicity of RFR was identified as the primary issue for investigation, consequently, a lifetime rodent carcinogenicity bioassay is a main component of the toxicology research program. In

recognition of the relationship between mutagenicity and carcinogenicity, the Research Agenda also included genotoxicity studies as a Tier I research priority.

Assay Selection Rationale: The WTR toxicology research program will initially focus on completion of studies utilizing standardized tests for the identification of genetic hazards. Included in this *in vitro* test battery will be the following mutation assays; *Salmonella typhimurium* (Ames) assay, *Escherichia coli* WP2uvrA reverse mutation assay, and the L5178Y TK± mouse lymphoma forward mutation assay. All three mutation assays are commonly used for screening of potential genetic hazards. Of the mammalian mutation assays available, the mouse lymphoma assay is preferred since the cells are normally grown in a suspension culture and it is likely to be a more sensitive assay. In addition, the “test battery” will include a chromosome aberration assay in human whole blood lymphocytes. The use of human lymphocytes as an *in vitro* cytogenetic assay as part of a standardized test battery is generally accepted. Peripheral blood lymphocytes are an easily obtainable, non-cycling, “normal” human cell type. Published reports on the response of human lymphocytes using the cytogenetic assays in “control” and exposed situations are readily available.

Statement of Work: Each assay will include an initial and confirmatory trial. Treatment groups will include, but not be limited to, appropriate negative and positive controls and three dose levels. Investigators must be capable of conducting all four assays and proposals must include information on each based on the requirements described below.

Special Requirements: Investigators should be aware that *in vitro* research sponsored by the WTR will be conducted at a single exposure facility. Details of the rationale for this decision are presented in the accompanying information. The logistics of utilizing this facility will be worked out with investigators selected for funding. Investigators submitting proposals should take into account the following requirements based on the use of a single exposure site: standard operating procedures (SOPs) must include a detailed list of required materials (i.e., flasks, media, etc.) for each assay; preliminary “control” experiments will be required to demonstrate that the investigator is capable of conducting the assay in this facility and is able to obtain results

consistent with historical positive and negative control values for their laboratory; technical staff will be required to stay at the facility throughout the conduct of the experiments and during data collection unless materials can be returned to the laboratory without affecting the outcome of the experiments and; principal investigators will be expected to be at the site at crucial phases of each of the assays.

Proposal Requirements: Proposals must include a statement of qualifications and details pertaining to experience with the *Salmonella*, *E coli*, mouse lymphoma, and human lymphocyte chromosome aberration assays using standardized techniques. An outline of protocols to be used, including SOPs for experimental techniques should be included. A detailed cost estimate including labor, expenses, equipment, and overhead must be included in the proposal. Applicants are required to demonstrate a thorough understanding of proposed assay systems, as well as consideration of the following required elements:

- (1) Method(s) for monitoring cell viability;
- (2) Demonstration of ability to achieve reproducible untreated control values for each assay;
- (3) Selection of appropriate positive controls for of the mammalian assays;
- (4) Consideration of protocols for assessing thermal stress;
- (5) Demonstration of GLP familiarity and previous compliance;
- (6) Procedures and equipment for data collection;
- (7) Procedures for statistical analysis including criteria for a positive response;
- (8) Consideration of the logistics related to use of the single site; and
- (9) Procedures for assessing reproducibility (intra- and inter-laboratory).

To assure reproducibility and consistency, more than one laboratory will be funded to perform each of the assays. Assay protocols and report formats must be based on those described in the Organization for Economic Cooperation and Development Guidelines (see Appendix B). All research will be conducted in accordance with GLP in collaboration with the WTR's Quality Assurance Unit. In addition, a commitment to publication of the results in the peer-reviewed scientific literature is required.

Submission Information: Applications in duplicate (facsimile transmissions will not be accepted) must be received by October 1, 1995:

Dr. G.L. Carlo, Chairman
Wireless Technology Research, L.L.C.
1711 N St., NW, Suite 200
Washington, DC 20036 USA

Please include reference number WTR-TRP-003.

7.2 Requests for Proposals - Tier II Epidemiology Studies

WTR seeks proposals from investigators to conduct epidemiology studies encompassing cohort and case-control designs to test specific hypotheses regarding cellular telephone use and disease. It is anticipated that potential investigators will be thoroughly familiar with all WTR background documents and will be responsive to the issues raised in them, as well as the issues raised in this document. Preference will be given to study teams who are multidisciplinary and can demonstrate strong understanding of biology, physics, and disease mechanisms as well as epidemiology and public health.

Proposals are requested for testing specific hypotheses regarding cellular telephones and disease in the following areas:

7.2.1 General Mortality and Morbidity Studies of Cohorts of Analog and Digital Cellular Telephone Users in the United States (WTR-EPI-003)

Subject Area: WTR, in response to the needs of its epidemiology research program, is soliciting proposals for specific research projects. The following background information and proposal details are intended to assist investigators interested in submitting proposals to conduct cohort studies of cellular telephone users and possible health outcomes relevant to exposure.

Background:

In August 1994, the SAG published a research plan entitled "Potential Public Health Risks from Wireless Technology: Research Agenda for the Development of Data for Science-Based Decisionmaking," hereafter referred to as the Research Agenda. The Research Agenda outlined guiding principles for the development of a complete, relevant, credible, and rigorous scientific program for the evaluation of potential human health risks associated with the use of wireless technology.

Guiding Principle Number One of the Research Agenda outlined a three-tiered concept to be used in evaluating the priorities of the risk evaluation research plan. Wide use of wireless communication instruments makes essential the inclusion of epidemiological data for the development of a high quality database to be used for possible post-market surveillance and a determination of potential health risks. Tier II studies will, therefore, include cohort and case-control studies for the evaluation of general and specific potential causal associations between wireless technology use and adverse effects on human health.

Rationale for cohort studies: Cohort studies will be used to evaluate morbidity and mortality among portable cellular telephone users. Both all cause and cause-specific outcomes will be examined for each cohort.

Proposal Requirements: Since there is no available cohort with measured RF exposure data, epidemiologist will have to use other, less quantitative exposure methods. Because cellular telephone companies compile accurate billing logs of all telephone calls, there is the potential to use billing data to identify cellular telephone customers and to classify them according to the amount of their usage. This can provide a surrogate for actual RF exposure. These data can then be linked with specific outcome databases in order to evaluate relevant causes of morbidity and mortality among the cohort. A pilot study of nearly 5,000 cellular phone subscribers conducted by Epidemiology Resources, Inc. has established a good correlation between answers supplied by the subscribers and their telephone billing records. Based on these results, we will accept the use of questionnaires to help quantify usage and address confounding issues in epidemiological studies. Epidemiology Resources, Inc. is the custodian of the billing records from the various cellular telephone carriers. Use of these records to define cohorts and quantify individual phone usage as part of epidemiological studies is encouraged; however, access to them must be coordinated through Epidemiology Resources, Inc.

Issues of potential biases from selection, misclassification and confounding should be addressed pro-actively. Sample size and power calculations should be included. A detailed rationale for interpretation of study results should be included and will be given significant weight during the

evaluation process. Proposals must include a statement of qualifications and details pertaining to experience in conducting cohort studies. An outline of study design and methodology including protocol details as well as detailed cost estimates including labor, expenses, equipment, and overhead must also be included in the proposal. Applicants are required to demonstrate a thorough knowledge of epidemiological concepts and biological endpoints, along with consideration of the following required elements:

- (1) Demonstration of ability to conduct general morbidity and mortality cohort studies;
- (2) Demonstration of Good Epidemiology Practice (GEP) familiarity and previous compliance;
- (3) SOPs for all routine procedures to be used;
- (4) Description of methods to be used in the collection and evaluation of exposure data;
- (5) Procedures for data collection;
- (6) Procedures for statistical analysis including criteria for a positive response; and
- (7) Description of and rationale for cohort selection including type of wireless technology(ies) to be included.

All research will be conducted in accordance with GEP in collaboration with the WTR's Quality Assurance Unit. In addition, a commitment to publication of results in the peer-reviewed scientific literature is required.

Submission Information: Applications in duplicate (facsimile transmissions will not be accepted) must be received by October 1, 1995:

Dr. G.L. Carlo, Chairman
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Please include reference number WTR-TRP-003.

7.2.2 General Mortality and Morbidity Studies of Cohorts of Digital Cellular Telephone Users in Europe (WTR-EPI-004)

Subject Area: WTR, in response to the needs of its epidemiology research program, is soliciting proposals for specific research projects. The following background information and proposal details are intended to assist investigators interested in submitting proposals to conduct cohort studies of cellular telephone users and possible health outcomes relevant to exposure.

Background: In August 1994, the SAG published a research plan entitled "Potential Public Health Risks from Wireless Technology: Research Agenda for the Development of Data for Science-Based Decisionmaking," hereafter referred to as the Research Agenda. The Research Agenda outlined guiding principles for the development of a complete, relevant, credible, and rigorous scientific program for the evaluation of potential human health risks associated with the use of wireless technology.

Guiding Principle Number One of the Research Agenda outlined a three-tiered concept to be used in evaluating the priorities of the risk evaluation research plan. Wide use of wireless communication instruments makes essential the inclusion of epidemiological data for the development of a high quality database to be used for possible post-market surveillance and a determination of potential health risks. Tier II studies will, therefore, include cohort and case-control studies for the evaluation of general and specific potential causal associations between wireless technology use and adverse effects on human health.

Rationale for cohort studies in Europe: Cellular telephone technology is slightly different in Europe than in the United States. Cellular telephones transmit either analog or digital voice messages, depending on the type of instrument and the service available. These technologies differ in that analog signals are continuous waves, and digital systems are pulsed. Because digital technology is more efficient in its use of channels, the industry is focusing on it for future use. Currently, in the United States simple analog frequency modulation (FM) technology is more prevalent; however, in Europe the current standard is the GSM technology which is digital. The

phones operate in a higher frequency range (between 890 and 960 MHZ) than those in the United States, and the power generated is higher on average.

In terms of outcome data, there are many well-maintained, large European databases available to examine a wide variety of possible health effects in a cohort of portable cellular phone users in Europe. Cohort studies will be used to evaluate morbidity and mortality among this cohort with both all cause and cause-specific outcomes examined.

Proposal Requirements: Since there is no available cohort with measured RF exposure data, epidemiologist will have to use other, less quantitative exposure methods. Because cellular telephone companies compile accurate billing logs of all telephone calls, there is the potential to use billing data to identify cellular telephone customers and to classify them according to the amount of their usage. This can provide a surrogate for all RF exposure. These data can then be linked with specific outcome databases in order to evaluate relevant causes of morbidity and mortality among the cohort. Questionnaire data can be used to supplement these cohort studies as needed to address confounding.

Issues of potential biases from selection, misclassification and confounding should be addressed pro-actively. Sample size and power calculations should be included. A detailed rationale for interpretation of study results should be included and will be given significant weight during the evaluation process. Proposals must include a statement of qualifications and details pertaining to experience in conducting cohort studies in Europe. An outline of study design and methodology including protocol details as well as detailed cost estimates including labor, expenses, equipment, and overhead must also be included in the proposal. Applicants are required to demonstrate a thorough knowledge of epidemiological concepts and biological endpoints, along with consideration of the following required elements:

- (1) Demonstration of ability to conduct general morbidity and mortality cohort studies in Europe;

- (2) Demonstration of Good Epidemiology Practice (GEP) familiarity and previous compliance;
- (3) SOPs for all routine procedures to be used;
- (4) Description of methods to be used in the collection and evaluation of exposure data;
- (5) Procedures for data collection;
- (6) Procedures for statistical analysis including criteria for a positive response; and
- (7) Description of and rationale for cohort selection including type of wireless technology(ies) to be included.

All research will be conducted in accordance with GEP in collaboration with the WTR's Quality Assurance Unit. In addition, a commitment to publication of results in the peer-reviewed scientific literature is required.

Submission Information: Applications in duplicate (facsimile transmissions will not be accepted) must be received by October 1, 1995:

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Please include reference number WTR-TRP-005.

7.2.3 Prospective Cohort Studies of Cellular Telephone Users Defined Along a Gradient of High, Medium, and Low Use (WTR-EPI-005)

Subject Area: WTR, in response to the needs of its epidemiology research program, is soliciting proposals for specific research projects. The following background information and proposal details are intended to assist investigators interested in submitting proposals to conduct cohort studies of cellular telephone users and possible health outcomes relevant to exposure.

Background: In August 1994, the SAG published a research plan entitled "Potential Public Health Risks from Wireless Technology: Research Agenda for the Development of Data for Science-Based Decisionmaking," hereafter referred to as the Research Agenda. The Research Agenda outlined guiding principles for the development of a complete, relevant, credible, and rigorous scientific program for the evaluation of potential human health risks associated with the use of wireless technology.

Guiding Principle Number One of the Research Agenda outlined a three-tiered concept to be used in evaluating the priorities of the risk evaluation research plan. Wide use of wireless communication instruments makes essential the inclusion of epidemiological data for the development of a high quality database to be used for possible post-market surveillance and a determination of potential health risks. Tier II studies will, therefore, include cohort and case-control studies for the evaluation of general and specific potential causal associations between wireless technology use and adverse effects on human health.

Rationale for cohort studies: Pilot studies have indicated that phone use varies considerably by geographic location. Cohort studies will be used to evaluate morbidity and mortality among portable cellular telephone users in specific cohorts of high, medium and low use. Both all cause and cause-specific outcomes will be examined for each cohort.

Proposal Requirements: Since there is no available cohort with measured RF exposure data, epidemiologist will have to use other, less quantitative exposure methods. Because cellular

telephone companies compile accurate billing logs of all telephone calls, there is the potential to use billing data to identify cellular telephone customers and to classify them according to the amount of their usage. This can provide a surrogate for all RF exposure. Billing records can also be valuable in assessing geographic areas of high, medium, and low use. These data can then be linked with specific outcome databases in these specific areas in order to evaluate relevant causes of morbidity and mortality among the cohort along a gradient of use. A pilot study of nearly 5,000 cellular phone subscribers conducted by Epidemiology Resources, Inc. has established a good correlation between answers supplied by the subscribers and their telephone billing records. Based on these results, we will accept the use of questionnaires to help quantify usage and address confounding issues in epidemiological studies. Epidemiology Resources, Inc. is the custodian of the billing records from the various cellular telephone carriers. Use of these records to define these specific cohorts and quantify individual phone usage as part of epidemiological studies is encouraged; however, access to them must be coordinated through Epidemiology Resources, Inc.

Issues of potential biases from selection, misclassification and confounding should be addressed pro-actively. Sample size and power calculations should be included. A detailed rationale for interpretation of study results should be included and will be given significant weight during the evaluation process. Proposals must include a statement of qualifications and details pertaining to experience in conducting cohort studies. An outline of study design and methodology including protocol details as well as detailed cost estimates including labor, expenses, equipment, and overhead must also be included in the proposal. Applicants are required to demonstrate a thorough knowledge of epidemiological concepts and biological endpoints, along with consideration of the following required elements:

- (1) Demonstration of ability to conduct general morbidity and mortality cohort studies at multiple sites;
- (2) Demonstration of Good Epidemiology Practice (GEP) familiarity and previous compliance;
- (3) SOPs for all routine procedures to be used;

- (4) Description of methods to be used in the collection and evaluation of exposure data;
- (5) Procedures for data collection;
- (6) Procedures for statistical analysis including criteria for a positive response; and
- (7) Description of and rationale for cohort selection including type of wireless technology(ies) to be included.

All research will be conducted in accordance with GEP in collaboration with the WTR's Quality Assurance Unit. In addition, a commitment to publication of results in the peer-reviewed scientific literature is required.

Submission Information: Applications in duplicate (facsimile transmissions will not be accepted) must be received by October 1, 1995:

Dr. G.L. Carlo, Chairman
Wireless Technology Research, L.L.C.
1711 N St., NW, Suite 200
Washington, DC 20036 USA

Please include reference number WTR-TRP-005.